

Long distance axon regeneration and functional recovery after spinal cord injury (SCI) in adult mice treated with C3.

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Inactivation of Rho GTPase in neurons allows for the growth of axons on inhibitory substrates. We demonstrate here, that Rho signalling inactivation by C3-transferase (C3) stimulates axon regeneration, upregulation of GAP-43 mRNA in neuronal cell bodies, and functional recovery of hindlimb movement after SCI in adult mice. After laminectomy and a dorsal hemisection of the spinal cord at T7, C3 was applied by a single local injection at the lesion site in a fibrin or collagen gel. Three weeks to three months post-lesion, the corticospinal tract (CST) of injured mice, was anterogradely labelled with WGA-HRP, and axon regeneration was detected in longitudinal cryostat sections of the spinal cord. The C3-treated animals showed sprouting of axons into the lesion site, and regenerated axons extended up to 12 mm distal to the lesion. Untreated animals showed retraction of CST axons from the lesion site. We assessed GAP-43 mRNA in the motor cortex by in situ hybridization on coronal brain sections. Untreated animals did not show any changes in GAP-43 mRNA expression, while mRNA levels increased in neurons of the motor cortex of C3-treated animals. Functional recovery was scored from 1-29 days after SCI using the BBB open field test. C3-treated animals showed a remarkable 24 hr recovery and continued to recover over next month with BBB scores significantly higher than untreated mice. These experiments demonstrate the potential of targeting signalling mechanisms converging to Rho to stimulate axon regeneration on inhibitory substrates in the adult CNS.

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Inactivation of Rho GTPase stimulates robust axon regeneration in transected spinal cord of adult mice.

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In the CNS of mammals, axon growth is blocked by growth inhibitory proteins present in myelin and in the glial scar. We have shown that inactivation of Rho GTPase in neurons allows axon growth on myelin (Lehmann et al, 1999 J. Neurosci. 19:7537) and on inhibitory chondroitin sulfate proteoglycans (CSPG). Here we investigate if inactivation of Rho by C3 enzyme stimulates regeneration of axons in the transected adult mouse spinal cord. C3 enzyme was applied to the injury site after thoracic dorsal hemisection or complete transection of adult mouse spinal cord. Three weeks or three months later the corticospinal tract was anterogradely labelled with WGA-HRP, and axon regeneration was detected in longitudinal cryostat sections of the spinal cord. We observed a massive sprouting of many corticospinal axons proximal the lesion, and axons extended past the lesion in white matter of the spinal cord. Regenerating axons grew long distances of >10 mm. Moreover, regenerating axons grew through the CSPG immunoreactive scar rather than around the lesion site. Our current studies are to examine the behavioural recovery associated with axon regeneration after complete transection of the spinal cord. These experiments demonstrate that targeting signalling mechanisms converging to Rho stimulates axon regeneration on inhibitory substrates in the adult CNS.

DESCRIPTOR(S)- *Enzymology (Biochemistry and Molecular Biophysics); *Nervous System (Neural Coordination); *mouse (Muridae) --adult; *Animals; *Chordates; *Mammals; *Nonhuman Mammals; *Nonhuman Vertebrates; *Rodents; *Vertebrates; *spinal cord --nervous system; *CNS central nervous system --nervous system; *myelin; * Rho GTPase; *axon regeneration

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